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| 10/713,898 | 10/18/2002 | David C. Schwartz | 960296.99047 | 4216 |

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| EXAMINER | |
|---|---|
| MUMMERT, STEPHANIE KANE | |
| ART UNIT | PAPER NUMBER |
| 1637 | |

| NOTIFICATION DATE | DELIVERY MODE |
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| 02/06/2009 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

pat-dept@quarles.com

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/713,898 | SCHWARTZ ET AL. | |
| | Examiner | Art Unit | |
| | STEPHANIE K. MUMMERT | 1637 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *25 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *21 and 23-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21 and 23-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/25/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Applicant's amendment filed on September 26, 2008 is acknowledged and has been entered. Claim 21 has been amended. Claim 22 has been canceled. Claims 21 and 23-27 are pending. Claims 1-20 and 28-33 are withdrawn from consideration as being drawn to a non-elected invention.

Claims 21 and 23-27 are discussed in this Office action.

All of the amendments and arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons discussed below. Any rejection not reiterated in this action has been withdrawn as being obviated by the amendment of the claims. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

**This action is made FINAL as necessitated by Amendment and IDS.**

**Previous Rejections**

***Claim Interpretation***

The term 'microchannel' is being given the broadest reasonable interpretation in light of the specification. The term is not explicitly defined in the specification and the term is instead described in general terms and includes preferred embodiments. For example, the specification notes "the present invention fixes and straightens polymeric molecules using a channel sized to provide laminar flow of a liquid along a channel length, the channel having at least a first wall

providing electrostatic attraction to the polymeric molecule" (paragraph 13 of PgPub). The specification also teaches "the channel may include a region of varying cross-section to promote a gradient in the laminar flow rate" (paragraph 29 of PgPub). Finally, regarding more specific dimensions, the specification notes "in one embodiment, the cross-sectional width of the micro-channel is 50 micrometers and is preferably less than 100 micrometers. More generally, it is believed that the width will be between one and one hundred times the straightened length 40 of the polymeric molecule" (paragraph 51 of PgPub). While this portion of the specification suggests specific size of the microchannel, this teaching does not reach to the level of a specific definition of the size at which a channel of the invention is a microchannel. Therefore, as the term has no specific size limitations associated with it, the term is being given the broadest reasonable interpretation and is being interpreted as reading on application of the method to a 'channel' of any size.

Regarding the term 'wall', the term is not given a specific definition and therefore is being given the broadest reasonable interpretation in light of the specification and is being interpreted as reading on DNA affixed or attached to any surface, including a rounded particle or bead.

***New Grounds of Rejection***

***Priority***

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or

provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 09/962802 (US Patent 6610256), 08/855410 (US Patent 6294136) and 08/415710 (US Patent 5720928), fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Each of these patent disclosures and claims are directed to practice of the method on a planar surface and do not disclose of otherwise provide support for the practice of the method in channel or microchannel formats as claimed in the instant specification. The only mention of channels or microchannels present in these prior filed applications is the use of a microchannel plate reader, a disclosure which does not support the method of straightening or fixing within a channel. While Applicant's mention of a laminar flowing chamber is noted, the specification of the priority documents specifically states "the laminar flow chamber should contain a thin space, for example, a space generated via 10-20 micron opening." This teaching is not the same as the micro-channel claimed. An opening with a "thin space" encompasses a narrow entry into a chamber with dimensions that widen to a size much larger than microns in dimension. Therefore, this teaching in the priority documents is not interpreted as sufficient to support a micro-channel.

Furthermore, it is also noted that the instant claims also require a step of "detaching the first wall from the micro-channel". This limitation is also lacking proper enabling support in the

priority documents. Therefore, the claims are being afforded the priority date of the instant application, October 18, 2002.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claims 21, 23-25 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shrewsbury et al. (International Conference on Modeling and simulation of Microsystems, Semiconductors, Sensors and Actuators, San Juan Puerto Rico, April 19-22, 1999, p. 578-580; IDS reference) in view of Bensimon et al. (US Patent 6,265,153; July 2001). Shrewsbury teaches a method of elongating DNA molecules in laminar flowing liquid as observed through epifluorescence microscopy (Abstract).

With regard to claim 21, Shrewsbury teaches a method of straightening and fixing polymeric molecules comprising the steps of:

(a) putting the polymeric molecules in a carrier liquid (p. 579, col. 1, where lambda-phage DNA is fluorescently labeled with YOYO1 and is present at a concentration of 0.05 ug/mL in a buffer comprising 10 mM Tris-HCl, 2 mM EDTA, 10 mM NaCl and 4% beta-mercaptoethanol),

(b) passing the polymeric molecules and carrier liquid through a micro-channel having a first wall to promote a laminar flow of carrier liquid in the micro-channel that elongates the

polymeric molecule and causes the polymeric molecule to achieve a straightened configuration (Abstract, p. 578, where it is noted that fluid flow is laminar and col. 2, 'subjecting DNA molecules to a uniform velocity gradient in a microchannel, we hope to lend insight into these phenomena' and 'experiments focus on the conformation of the DNA molecule as it is pumped through the device channels'; legend, Figure 2, 'stretching of DNA with increasing velocity').

With regard to claim 24, Shrewsbury teaches an embodiment of claim 21 further including the step of (d) optically inspecting the straightened polymeric molecule attached to the first wall (Figure 2, where stretched DNA is observed using epifluorescence microscopy "at a variety of flow rates").

With regard to claim 25, Shrewsbury teaches an embodiment of claim 21 further wherein step (b) first causes a straightening of the polymeric molecule in the laminar flow and third causes attachment of the length of the polymeric molecule to the wall (Figure 2, where stretched DNA is observed using epifluorescence microscopy "at a variety of flow rates").

Regarding claims 21, 24 and 25, while Shrewsbury does not teach direct attachment to the first wall of the channel, Bensimon teaches a process for aligning a macromolecule onto the surface of a support and attaching the molecule to the first wall (Abstract).

With regard to claim 21, Bensimon teaches having a first wall electrostatically attractive to the polymeric molecule (col. 3, lines 58-65, where the adsorption of the macromolecule onto the surface can be controlled through surface charges and the electrostatic interactions between the surface and the molecule; col. 4, lines 52-61, where specific types of surface functionalities are described; see also col. 5, lines 4-23, for example) and causing the polymeric molecule to adhere in straightened configuration to the first wall (Example 1, col. 17, lines 39-46, where

capillary force on the DNA molecule(s) is sufficient to stretch the molecule; col. 4, lines 4-6, where it is noted that one aligned, the molecules adhere strongly to the surface).

With regard to claim 25, Bensimon teaches an embodiment of claim 21, wherein second causes attachment of one end of the polymeric molecule to the first wall (col. 3, lines 58-65, where the adsorption of the macromolecule onto the surface can be controlled through surface charges and the electrostatic interactions between the surface and the molecule).

With regard to claim 27, Bensimon teaches an embodiment of claim 21 further including the step of treating at least one wall of the microchannel to have a positive surface charge of predetermined density (col. 3, lines 58-65, where the adsorption of the macromolecule onto the surface can be controlled through surface charges and the electrostatic interactions between the surface and the molecule; col. 4, lines 52-61, where specific types of surface functionalities are described; see also col. 5, lines 4-23, for example).

With regard to claim 23, Bensimon teaches an embodiment of claim 21 further including the step of (d) applying restricting enzymes to the straightened polymeric molecule attached to the first wall (col. 12, lines 53-58, where physical mapping of genomic DNA can be carried out through a method comprising the steps of extraction, purification, cleavage with restriction enzyme followed by 'combing' on surfaces).

Regarding claim 23, Bensimon teaches that the method of physical mapping of polymeric molecules comprises thorough restriction digestion followed by fixation and elongation. However, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the order of method steps taught by Bensimon to arrive at the claimed invention with a reasonable expectation of success. As noted in the MPEP § 2144.04 IV

C, "Ex parte Rubin , 128 USPQ 440 (Bd. App. 1959) (Prior art reference disclosing a process of making a laminated sheet wherein a base sheet is first coated with a metallic film and thereafter impregnated with a thermosetting material was held to render prima facie obvious claims directed to a process of making a laminated sheet by reversing the order of the prior art process steps.). See also In re Burhans, 154 F.2d 690, 69 USPQ 330 (CCPA 1946) (selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results); In re Gibson, 39 F.2d 975, 5 USPQ 230 (CCPA 1930) (Selection of any order of mixing ingredients is prima facie obvious.)." Therefore, in the absence of new or unexpected results, it would have been prima facie obvious to one of ordinary skill in the art to adjust the order of the method steps taught by Bensimon to arrive at the claimed invention with a reasonable expectation for success.

Further regarding claim 21, neither Shrewsbury or Bensimon explicitly teach the term of "detaching" the first wall from the microchannel. Bensimon teaches analysis of the straightened polymeric molecules stretched out on a slide or other planar surface (Example 3, col. 19, lines 21-26, where the adhered molecules are analyzed after removal of the coverslip; see also Figures 7-9). Therefore, it would have been prima facie obvious to remove the slide or planar support with the straightened molecules attached for further processing, achieving the limitation of the claim as recited.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have applied the teachings of Bensimon to the method of DNA stretching and analysis taught by Shrewsbury to arrive at the claimed invention with a reasonable expectation for success. Shrewsbury teaches a method comprising "subjecting DNA molecules

to a uniform velocity gradient in a microchannel" and "experiments focus on the conformation of the DNA molecule as it is pumped through the device channels" (p. 578, col. 1, Introduction and Materials and Methods). Shrewsbury also notes "under laminar flow conditions, the shear rate is highest at the channel walls and lowest at the channel centerline. Hence, on average, one expects to observe relatively stretched conformations near the walls and coiled conformations near the centerline" (p. 579, col. 2). While Shrewsbury does not teach attachment to the wall, Bensimon teaches a very similar method of DNA analysis, however an end of the DNA is fixed and the DNA is aligned along the length of a wall, through progress of a meniscus instead of by laminar flow.

In view of the common teachings between Bensimon and Shrewsbury, it would have been prima facie obvious to one of ordinary skill in the art to incorporate the format of a surface electrostatically attractive to a polymeric molecule to promote both adherence and straightening of polymeric molecules as taught by Bensimon into the format taught by Shrewsbury. Furthermore, while it is noted that neither Bensimon or Shrewsbury explicitly teach the term detachment of a wall or bead from within a channel, it was well known to one of ordinary skill in the art at the time the invention was made how to remove a bead or other type of surface, particularly with DNA attached, from a support, for further processing or analysis. Both Bensimon and Shrewbury teach the inclusion of glass coverslips (p. 579, col. 1). Bensimon specifically teaches "the combed YACs are denatured between two cover slips" and "the detection of hybrids is performed according to procedures known for in situ hybridizations" and "hybridized segments such as that shown in Fig. 10 are then observed by fluorescence microscopy" (Example 3, col. 19, lines 38-50). Therefore, despite the lack of specific teaching

of the word detachment or detaching, it would have been prima facie obvious based upon the teaching of Bensimon of the desirability of having the stretched polymers or oligonucleotides present in a format available for further processing, analysis and detection, and therefore separate from the channel or means for separation. It also would have been prima facie obvious to envision a channel for straightening molecules using techniques including Bensimon and Shrewsbury, and to include a format wherein the stretched DNA could be removed for further analysis while stretched on the surface. Therefore, as each of these elements were known in the prior art at the time of the invention and the combination of these elements would provide a predictable result, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have incorporated these elements to analyze straightened DNA molecules and then to recover these molecules following analysis through the removal of the bead or wall element from the other portions of the channel or support.

2. Claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over Shrewsbury in view of Bensimon as applied to claims 21, 23-25 and 27 above, and further in view of Kaiser et al. (Journal of Molecular Biology, 1963, vol. 6, p. 141-7). Shrewsbury teaches a method of elongating DNA molecules in laminar flowing liquid as observed through epifluorescence microscopy (Abstract).

With regard to claim 26, Kaiser teaches an embodiment of claim 21 wherein the polymeric molecules are treated with a condensation agent to collapse the polymeric molecules into shear resistant balls and wherein step (a) includes the step of placing the polymeric molecules and carrier liquid into a reservoir attached to the micro-channel and decondensing the

polymeric molecules in the reservoir prior to step (b) (Table 1, where specific concentrations of spermine are disclosed and p. 142, 'materials and methods' heading where DNA was isolated from bacteriophage λ and incorporated into the assay; p. 146, where it is noted that the protective effect may result from the formation of soluble aggregates).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have included the teachings of Kaiser, regarding the protection of nucleic acids through the inclusion of spermine to the method of DNA stretching and analysis taught by Shrewsbury and Bensimon to arrive at the claimed invention with a reasonable expectation for success. As taught by Kaiser, "Spermine markedly protects DNA from breakage by rapid stirring" (Abstract, line 1). Kaiser also teaches that "When λ DNA was stirred in the presence of spermine as shown in Table 1 neither the infectivity nor the ratio of turbid plaques to total plaques changed from their initial values." (p. 144, top paragraph). Finally, Kaiser concludes that "the data presented above show that polyamines, spermine in particular, protect λ DNA from breakage by rapid stirring" (p. 146, 'discussion' heading). The method taught by Shrewsbury notes "the rotation of the DNA molecule as it flows through the channel is problematic at increased DNA concentrations when the separation between molecules decreases and the molecular chains are susceptible to entanglement and possibly shearing" (p. 580, col. 1). Shrewsbury also notes that "the relationship between flow rate and the 'average' DNA length (averaged over many starting conformations and over the tumbling of the chain') is under investigation" (p. 580, col. 2). Considering these teachings, Shrewsbury expresses motivation to maintain the polymer sequence in an intact linear format in order to facilitate the measurements regarding the length and flow rate analyses. Therefore, Shrewsbury would have been motivated

to incorporate solvents or steps directed specifically to the protection of the nucleic acid from breakage prior or during stretching. Considering the teachings of Kaiser towards the protective effects of spermine on DNA, one of ordinary skill in the art at the time the invention was made would have been motivated to incorporate spermine as taught by Kaiser into the method of DNA stretching and analysis taught by Shrewsbury and Bensimon to achieve intact molecules prior to and during stretching and analysis.

### *Response to Arguments*

Applicant's arguments with respect to claims 21 and 23-27 have been considered but are moot in view of the new ground(s) of rejection.

### *Relevant Prior Art*

3. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Chan et al. (US Patent 6,696,022; February 2004) teaches stretching of long DNA molecules using flow in channels (Abstract).

### *Conclusion*

No claims are allowed.

Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on September 25, 2008 prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See

MPEP § 609.04(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEPHANIE K. MUMMERT whose telephone number is (571)272-8503. The examiner can normally be reached on M-F, 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Stephanie K. Mummert/
Examiner, Art Unit 1637

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